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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/539,229	04/27/2006	John William Chapman	056159-5261	6003

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MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

EXAMINER

STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
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1656

MAIL DATE	DELIVERY MODE
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01/22/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/539,229

Applicant(s)

CHAPMAN ET AL.

Examiner

David J. Steadman

Art Unit

1656

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 October 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-13 is/are pending in the application.
- 4a) Of the above claim(s) 10 and 11 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-9, 12 and 13 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 16 June 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 6/16/05.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

- [1]** Claims 1-13 are pending in the application.

Election/Restriction

- [2]** Applicant's election of Group I, claims 1-9 and 12-13, in the reply filed on 10/30/07, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

- [3]** Claims 10-11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on 10/30/07.

Claim to Priority

- [4]** This application is a 371 filing of PCT/EP03/12219, filed on 11/3/03 and claims foreign priority under 35 USC § 119(a)-(d) to EPO 02258921.2, filed on 12/20/02. A certified copy of the foreign priority document was filed in the instant application on 6/16/05.

Information Disclosure Statement

[5] All references cited in the IDS filed on 6/16/05 have been considered by the examiner as evidenced by the examiner's initials and signature. A copy of Form PTO-1449 is attached to the instant Office action.

Claim Objections

[6] Claims 6-7 are objected to in the recitation of "pmt1" and "pmt2". Abbreviations, unless otherwise obvious and/or commonly used in the art, e.g., DNA, should not be recited in the claims without at least once reciting the entire phrase for which the abbreviation is used. Appropriate correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[7] Claims 1-8 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which appellant regards as the invention.

According to MPEP 2173.05(a), "The meaning of every term used in a claim should be apparent from the prior art or from the specification and drawings at the time the application is filed". MPEP 2173.05(b) states, "A claim may be rendered indefinite by reference to an object that is variable". Claim 1 (claims 2-8 and 12 dependent therefrom) is indefinite in the recitation of "a type III antifreeze protein" as it is unclear as to the intended scope of proteins that are encompassed by the noted phrase. According

to the specification at pp. 8-9, "For the purposes of this invention, an antifreeze protein is a protein which has significant ice recrystallisation inhibition properties and is therefore an ice structuring protein...The antifreeze proteins according to the present invention are type III AFPs. These AFPs have to date been identified in a number of polar fish of the family Zoarcidae such as *Macrozoarces americanus* (Eel pout, Ocean pout) and *Anarhichas lupus* (Wolf fish)--Barrett, 2001, Int. J. Biochem. Cell Biol. 33: 105-117. Type III AFPs typically have a molecular weight of from about 6.5 to about 14 kDa, a beta sandwich secondary structure and a globular tertiary structure. A number of genes encoding type III AFPs have been cloned (Davies and Hew, 1990, FASEB J. 4: 2460-2468). A particularly preferred type III AFP is type III HPLC-12". However, even in view of this "definition", it remains unclear as to what features distinguish those AFPs that are considered to be "type III" AFPs from those that are not, particularly as the specification's noted "definition" is non-limiting and/or exemplary. In this case, it would appear that the prior art suggests that there are no distinguishing features of a type III AFP. For example, according to the prior art reference of Davies et al. (FASEB J. 4:2460-2468, 1990), "type III" AFPs "lack[] distinctive features in its composition and sequence" (p. 2460, column 2, bottom). It is suggested that applicant clarify the meaning of the noted phrase, particularly with respect to how a skilled artisan distinguishes a "type III" AFP from any other AFP, e.g., type I or type II AFPs.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[8] Claims 1-9 and 12-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

According to MPEP 2163.II.A.1, in evaluating a claimed invention for adequate written description, the examiner should determine what the claim as a whole covers. "Claim construction is an essential part of the examination process. Each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description. See, e.g., *In re Morris*, 127 F.3d 1048, 1053-54, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997)."

The claims are drawn to a method for recombinantly producing a genus of type III antifreeze proteins (AFP) in a genus of fungal host cells that are deficient in protein glycosylation. The dependent claims limit the genus of type III AFP polypeptides or the genus of protein glycosylation-deficient fungal host cells. In construing the scope of "type III antifreeze protein", it is noted that the specification states, "For the purposes of this invention, an antifreeze protein is a protein which has significant ice recrystallisation inhibition properties and is therefore an ice structuring protein... The antifreeze proteins

according to the present invention are type III AFPs...Type III AFPs typically have a molecular weight of from about 6.5 to about 14 kDa, a beta sandwich secondary structure and a globular tertiary structure" (specification at p. 8, lines 7 to 30). In construing the term "HPLC-12", the specification states, "Type III HPLC-12 polypeptides according to the present invention include polypeptides having the amino acid sequence shown as SEQ ID NO:1 and functional equivalents thereof...By "functional equivalent" is meant any polypeptide whose sequence has at least 80%, more preferably at least 85%, 90% or 95% sequence identity with the sequence of type III HPLC-12 as shown in SEQ ID NO: 1 and which exhibits AFP activity, in particular ice recrystallisation inhibitory (RI) activity. It is preferred that functional equivalents have at least 50% of the RI activity of a polypeptide having the amino acid sequence of type III HPLC-12 as shown in SEQ ID No:1, more preferably at least 60%, 70% or 80% of the RI activity of a polypeptide having the amino acid sequence of type III HPLC-12 as shown in SEQ ID No:1. RI activity can be conveniently be measured by means of a modified splat assay, as described in WO 00/53029" (p. 9, lines 6 to 21). In construing the term "fungal host cell which is deficient in protein glycosylation", the examiner notes the specification's disclosure at pp. 13-14.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or

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disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses only a single representative species of the recited genus of type III AFPs, including HPLC-12 proteins, *i.e.*, SEQ ID NO:1, and only a single representative species of glycosylation-deficient fungal cells that can be used for type III AFP production, *i.e.*, a *Saccharomyces cerevisiae* having a deletion of the *pmt1* and/or *pmt2* genes. The specification fails to describe any additional representative species of the recited genus type III AFPs or HPLC-12 proteins or fungal host cells. While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus," it also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus." In the instant case, the recited genus of type III AFPs and HPLC-12 polypeptides encompasses species that are widely variant, encompassing any polypeptide considered to be a type III AFP or HPLC-12 polypeptide from any source having any sequence of amino acids, including mutants and variants thereof. Also, the genus of fungal cells encompasses widely variant cells, having any alteration that results in the fungal host being deficient in protein glycosylation. In this case, the disclosure of the single representative species of

type III AFPs or HPLC-12 polypeptides or fungal host cells as noted above is insufficient to be representative of the attributes and features of all species as encompassed by the claims.

Given the lack of description of a representative number of polypeptides, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[9] Claims 1-9 and 12-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for recombinantly producing an Ocean Pout type III AFP HPLC-12 peptide in a *Saccharomyces cerevisiae* host with an inactivated pmt1 and/or pmt2 gene, does not reasonably provide enablement for a method for recombinantly producing any type III AFP polypeptide using any fungal host that is deficient in protein glycosylation as broadly encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

"The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the

claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: According to MPEP 2164.04, "[b]efore any analysis of enablement can occur, it is necessary for the examiner to construe the claims...and explicitly set forth the scope of the claim when writing an Office action." Also, MPEP 2164.08 states, "[w]hen analyzing the enabled scope of a claim, the teachings of the specification must not be ignored because claims are to be given their broadest reasonable interpretation that is consistent with the specification."

As noted above, the claims encompass production of any polypeptide considered to be a "type III AFP" wherein the structure and source of the polypeptide is essentially unlimited, and includes mutants and variants. Also as noted above, the scope of "HPLC-12" polypeptides encompasses "polypeptides having the amino acid sequence shown as SEQ ID NO:1 and functional equivalents thereof...By "functional equivalent" is meant any polypeptide whose sequence has at least 80%, more preferably at least 85%, 90% or 95% sequence identity with the sequence of type III HPLC-12 as shown in SEQ ID NO: 1 and which exhibits AFP activity, in particular ice recrystallisation inhibitory (RI) activity". The term "fungal host cell which is deficient in protein glycosylation", encompasses essentially any fungal host that has reduced protein glycosylation,

wherein the reduction in protein glycosylation is achieved by any method. The enablement provided by the specification is not commensurate in scope with the claims with regard to the "type III AFP" and "HPLC-12" polypeptides and fungal host cells as broadly encompassed by the claims. In this case, the specification is enabling only for a method for recombinantly producing an Ocean Pout type III AFP HPLC-12 peptide in a *Saccharomyces cerevisiae* host with an inactivated pmt1 and/or pmt2 gene.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: Regarding the ability for recombinantly producing any type III AFP in a fungal host, it is noted that according to Chapman et al. (WO 97/02343; cited in the IDS filed on 6/16/05), all fungally produced isoforms of Ocean Pout type III AFP with the exception of HPLC-12 failed to show "significant antifreeze activity" (p. 33, bottom). As such, it is highly unpredictable as to whether or not any fungally-produced type III AFP will exhibit antifreeze activity.

Regarding the scope of "type III AFP" and "HPLC-12" polypeptides, it is noted that the amino acid sequence of a protein determines its structural and functional properties. Predictability of which changes can be tolerated in an encoded protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. The positions within a protein's sequence where modifications can be made with a reasonable expectation of success in obtaining a polypeptide having the desired

activity/utility are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g., multiple substitutions. In this case, the necessary guidance has not been provided in the specification as explained in detail above. Thus, a skilled artisan would recognize the high level of unpredictability in making the entire scope of recited polypeptides. The high level of unpredictability is evidenced by Branden et al. ("Introduction to Protein Structure", Garland Publishing Inc., New York, 1991) teaches "[p]rotein engineers frequently have been surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he often surprising results of such experiments reveal how little we know about the rules of protein stability... they also serve to emphasize how difficult it is to design *de novo* stable proteins with specific functions" (page 247) and Witkowski et al. (Biochemistry 38:11643-11650, 1999), which teaches a single amino acid change in a protein's sequence alters the protein's activity. In view of the unpredictable nature of amino acid substitution, it follows that the effects of such substitution(s) in any and all proteins involved in protein glycosylation in a living fungal host are also unpredictable.

The amount of direction provided by the inventor and The existence of working examples: In this case, the specification discloses only two working examples of the claimed method, *i.e.*, a method for recombinantly producing an Ocean Pout type III AFP HPLC-12 peptide in a *Saccharomyces cerevisiae* host with an inactivated pmt1 or pmt2 gene. The specification fails to disclose any guidance for using any other fungal host for

recombinant production of any other type III AFPs with an expectation that the fungally-produced type III AFP polypeptide will maintain antifreeze activity.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods for recombinant protein expression of heterologous proteins using a fungal host cell were well-known in the prior art at the time of the invention, it was not routine to use any fungal host cell, altered by any method to achieve deficient protein glycosylation, to recombinantly express any type III protein as broadly encompassed by the claims.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required, undue experimentation is necessary for a skilled artisan to make and use the entire scope of the claimed invention. Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

[10] Claim(s) 1-9 and 12-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chapman et al. (WO 97/02343; cited in the IDS filed on 6/16/05; "Chapman") in view of Ng et al. (US Patent Application Publication 2002/0068325; "Ng") and Gentzsch et al. (*FEBS Lett.* 377:128-130, 1995; "Gentzsch"). The claims are drawn to a method for recombinantly producing a type III AFP in a fungal host cell that is deficient in protein glycosylation.

Chapman teaches a method for recombinantly producing an Ocean Pout type III AFP HPLC-12 peptide in a *Saccharomyces cerevisiae* host trasfected with a vector encoding said peptide. See Example 5 at pp. 35-37. Chapman does not teach or suggest the use of a pmt1- or pmt2-deficient strain of *S. cerevisiae* for use in the disclosed method.

Ng teaches "In yeast, O-linked glycosylation begins in the ER through the action of a family of genes called protein mannosyltransferases (PMT)" (paragraph 68 at p. 6); teaches pmt1 and pmt2 mutant *S. cerevisiae* strains, with inactivated pmt1 and pmt2 genes, respectively (paragraph 57 at p. 4); and teaches "These data show that heterologous proteins expressed in yeast are inappropriately modified by O-linked glycosylation. In turn, the modification can have negative consequences on the

maturation and activity of the protein. The inventors have established that coupling expression using an endogenous signal sequence with specific mutant strains deficient in O-linked glycosylation, the activity of heterologous proteins expressed in yeast can be drastically improved. Since there are 6 PMT genes in yeast that are non-redundant and exhibit differences in substrate specificity, deletion strains of any of the six genes may provide the needed inhibition of aberrant O-glycosylation. In addition, mutations can be combined to further promote proper folding. Thus the inventors have developed a novel solution for overcoming a problem that has limited the potential of low cost expression of commercially important molecules in yeast" (paragraph 71 at p. 6).

Gentzsch teaches pmt1 and pmt2 deletion mutants of *S. cerevisiae* (p. 28, column 2, paragraph 2.1); teaches the polypeptides encoded by pmt1 and pmt2 function as a heterodimer having O-mannosyltransferase activity in the O-glycosylation of polypeptides (p. 128, abstract); and teaches that disruption of each of these genes leads to "a dramatic decrease of mannosyltransferase activity in vitro" (p. 128, abstract).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Chapman, Ng, and Gentzsch to modify the method of Chapman to use a pmt1- and/or a pmt2-deficient strain of *S. cerevisiae*. One would have been motivated to do this because of the advantages of using such a strain as noted by Ng above. One would have had a reasonable expectation of success for modifying the method of Chapman to use a pmt1- and/or a pmt2-deficient strain of *S. cerevisiae* because of the results of Chapman, Ng, and Gentzsch. Therefore, claims 1-9

and 12-13, drawn to a method as described above, would have been obvious to one of ordinary skill in the art at the time of the invention.

Citation of Relevant Prior Art

[11] The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Van de Laar et al. (WO 2002/048382) teaches recombinant production of ocean pout HPLC12 antifreeze protein as described in Chapman (WO 97/02343) as noted above. See pp. 15-23, particularly p. 16, lines 7-8. The teachings of the Van de Laar reference are cumulative to the teachings of the Chapman reference and therefore, in the interest of brevity the Van de Laar reference has not been applied in a prior art rejection.

Conclusion

[12] Status of the claims:

- Claims 1-13 are pending.
- Claims 10-11 are withdrawn from consideration.
- Claims 1-9 and 12-13 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Steadman/
David J. Steadman, Ph.D.
Primary Examiner
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